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ORIGINAL RESEARCH article

Development and evaluation of muco-adhesive buccal films containing metronidazole for the treatment of periodontal diseases

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Abstract: Gingivitis, a reversible inflammation of the gums leads to an advancement to periodontitis, a more severe and often irreversible stage characterized by the destruction of connective tissue and bone, potentially leading to tooth loss. This study was designed to develop and evaluate muco-adhesive buccal films containing metronidazole for localized treatment of periodontal disease, aiming to reduce systemic side effects and improve therapeutic efficacy. Thin films were prepared using chitosan as the primary polymer, combined with various copolymers (HPMC, MC, EC, PVP, HPC, and Carbopol) via the solvent casting technique. Thirteen formulations (F1-F13) were investigated for their ability to control the *in vitro* drug release, surface pH, folding endurance, drug content uniformity, and muco-adhesion, in addition to studying drug release kinetics. Formulations F12 (60.0% HPMC, 20.0% chitosan) and F13 (20.0% HPMC, 60.0% chitosan) showed optimal surface pH (≈6.7-7.0) with high muco-adhesion characteristics (49-51 Mn/m). Sustaining or expediting the drug release rate was manipulated by tailoring the polymer composition within the studied formulations. Examining drug release data has shown that the release kinetics followed the Korsmeyer-Peppas model, indicating diffusion and polymer relaxation mechanisms. The study demonstrates that polymer selection, in addition to the chosen ratio allows customization of release kinetics, Formulation F9 (20.0% HPC, 60.0% Chitosan) was proven to have the ability to provide the most sustained release characteristics. These findings support the potential of chitosan-based muco-adhesive films as effective localized delivery systems for metronidazole in periodontal therapy.

Introduction

Periodontal disease encompasses a group of chronic inflammatory conditions that progressively destroy the tooth-supporting structures, including the gingiva, periodontal ligaments, root cementum, and alveolar bone [1]. These pathologies are primarily driven by localized infections involving anaerobic gram-negative bacteria [2]. The American Association of Periodontology classifies these into two main categories: gingivitis and periodontitis, based on the extent of tissue involvement [3]. As highly prevalent global health issues, they begin with gingivitis, a reversible inflammation of the gums. If left untreated, this leads to an advancement to periodontitis, a more severe and often irreversible stage characterized by the destruction of connective tissue and bone, potentially leading to tooth loss [4]. The primary etiological factor for both conditions is the accumulation of bacterial plaque [3, 5]. Consequently, standard treatment protocols combine mechanical plaque removal with adjunctive antimicrobial therapy [1, 4, 6].

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Metronidazole (MTZ) is a cornerstone antibiotic in managing periodontal infection due to its pronounced efficacy against obligate anaerobes, such as *Porphyromonas gingivals*, its broad-spectrum antibacterial and antiprotozoal activity [3], coupled with a low minimum inhibitory concentration, solidifies its status as first-line therapeutic agent [7]. The conventional oral regimen for ulcerative gingivitis is 200 mg administered three times daily for three days, while a 25.0% dental gel is available for topical application in chronic cases. MTZ undergoes hepatic metabolism and has a half-life of 6-7 hr [8]. However, systemic administration of MTZ is associated with a range of adverse effects, including gastrointestinal disturbances, neurological symptoms, disulfiram like reaction with alcohol, potentiation of warfarin, leucopenia, neutropenia, peripheral neuropathy, and central nervous system toxicity [9, 10]. To minimize these systemic side effects, a promising strategy is to reduce the administered dose through localized drug delivery. Buccal mucoadhesive systems offer a targeted approach, enabling the application of a lower drug dose directly to the affected site. This method achieves high local concentrations while minimizing systemic exposure and associated adverse reactions [8, 10]. A dose as low as 20 mg of MTZ has been shown to be effective via this route [4]. Buccal drug delivery enables direct absorption into systemic circulation via the internal jugular vein, thereby bypassing hepatic first-pass metabolism and degradation in the gastrointestinal tract. This significantly enhances drug bioavailability and allows for substantial dose reduction without compromising therapeutic efficacy [11, 12]. An ideal buccal delivery system must possess robust bio-adhesive properties to ensure prolonged retention in the oral cavity, precise localization, and controlled drug release. Through muco-adhesion, the formulation maintains prolonged contact with the oral mucosa, thereby enhancing antibiotic concentration at infection sites while minimizing systemic exposure [13-15]

Chitosan, a biocompatible, biodegradable, and non-toxic polymer derived from chitin, has attracted significant interest in pharmaceutical applications. Its excellent film-forming, mucoadhesive, and antimicrobial properties, along with its wound-healing capacity, make it an ideal candidate for designing drug delivery systems aimed at the gingival margin and periodontal pockets [16, 17]. Thus, this study was undertaken to design, develop, and evaluate mucoadhesive buccal films of MTZ. A variety of polymers, including chitosan, Hydroxy Propyl Methyl Cellulose (HPMC), Methyl Cellulose (MC), Carbopol, and hydroxy propyl cellulose (HPC). were employed. The films were fabricated using a simple solvent casting technique without the use of any harmful organic solvents. The prepared films were characterized for their physical parameters, and potential interactions between drug and polymers were investigated to ensure formulation quality.

Materials and methods

Fabrication of films: Periodontal films were prepared by the solvent casting method [15]. The films were prepared as per the formula given in **Table 1**. Accurately weighed quantity of chitosan was dissolved in accurately measured volume of 1.0% lactic acid and the required quantity of either PVP, HPC, EC, HPMC, Carbopol, or MC was dissolved in distilled water and then added to chitosan solution with continues stirring to obtain a homogeneous solution of formulations F1 to F13 (EC was dissolved in 20 ml ethanol), and the required amount of MTZ (20.0% w/w) was added to the formed solution and stirred for 15 min. The films were casted by pouring 5.0 ml of each polymeric solution in glass petri dishes which were left in the hood allowing the solvent to evaporate at room temperature. Each formulation was prepared in triplicate. Dry thin films were obtained after 48 hrs and stored in a desiccator.

In vitro drug release: The *in vitro* drug release studies were carried out using a USP type II dissolution paddle apparatus, Erweka. 350 ml of distilled water previously equilibrated at 37.0±1.0˚C were added to each beaker of the apparatus, followed by careful immersion of petri dishes with test films adhered to the bottom. The paddle's speed was set at 50 rpm. 3.0 ml samples were collected at time intervals of 0.5, 1.0, 2.0, and 3.0 hr, till complete release was achieved. Each sample was replaced with the same volume of fresh dissolution

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medium to maintain the volume constant, therefore, maintaining the sink condition. The withdrawn samples were filtered through 0.45-µm membrane filters [18]. Samples were analyzed using a UV spectrophotometer at a wavelength of 320.5 nm [19].

Table 1: Composition of formulations F1-F13 (%W/W)

Ingredients	Composition of formulations F1-F13 (%W/W)												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Chitosan (%)	80	60	20	20	60	60	20	20	60	40	20	20	60
MC (%)				60	20					20	40		
EC (%)		20	60										
PVP (%)						20	60						
HPC (%)								60	20				
Carbopol (%)										20	20		
HPMC (%)												60	20
1.0% lactic acid (ml)	30	30	30	30	30	30	30	30	30	20	20	20	20
Distilled water (ml)										10	10	10	10
Ethanol (ml)		10	10										
Metronidazole (%)	20	20	20	20	20	20	20	20	20	20	20	20	20

Folding endurance: As described by Khanna et al. [20], the folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times it is folded in the same place without any breakage or tearing gives a value of the folding endurance. This test was done on all the films five times.

Determination of film thickness and studying the effect of film thickness on the drug release profile: Films of different thicknesses of formulation F13 were prepared by pouring 5.0 ml, 7.0 ml, and 9.0 ml of the polymeric solution into glass Petri dish (diameter 4.5 cm). After 24 hr of ambient drying, the resulting films were stored between two sheets of wax paper. Each thickness measurement was carried out at multiple points using a digital micrometer, and the average reading was calculated for three films per formulation. Drug release studies were then conducted on these films with different thicknesses to analyze the effect of film thickness on the release profile [18, 21].

Film surface pH study: Periodontal films were left to swell in the presence of 5.0 ml of double water for 2.0 hr in a glass petri dish and then the pH was measured by bringing a combined glass electrode of the portable pH meter near the surface of the thin film and noting the reading as a meter was stable [22].

Fourier Transform Infrared (FTIR) spectroscopic studies: FTIR spectra of samples were taken on a Shimadzu instrument to investigate the possible interaction between the drug and excipients. The samples were crushed with KBr to get the pellets by applying a pressure of 300 kg cm^{-2}. FTIR studies of MTZ, chitosan and HPMC, and its formulation (A1=F12) and A2 (F13) were recorded using an FTIR Spectrophotometer, in the range between 4000 and 400 cm^{-1} [7].

In vitro release kinetics: In vitro release kinetic modeling was evaluated by DDsolver®. The mode of MTZ release from prepared films was decided on the basis of the best fit model, either zero order, first order, Higuchi or Korsmeyer-Peppas models [22].

Drug content uniformity of films: Film portion (size of 4.0 cm^2) was taken from different areas of prepared films and placed in a 10.0 ml volumetric flask; 10.0 ml of ethyl alcohol was added and kept aside till the film dissolves completely. From this solution, 1.0 ml was pipetted out and diluted to 10.0 ml with double distilled water. The UV absorbance of the solution was measured at 320.4 nm. The polymer solution without the drug serves as a blank. In case of HPMC film, a combination of water and alcohol is used to dissolve the film [23].

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In vitro muco-adhesion test. A bio-adhesive film, mounted with scotch tape onto a stainless-steel disk attached to a tensiometer's force gauge, was brought into contact with the mucosal surface for 2.0 min. The film was then slowly pulled off, and the tensile strength required for detachment (measured in Mn/m using the tensiometer) was recorded as the bio-adhesion force [18].

Statistical analysis: The test of significance and lack of significance among treatments at a 95.0% confidence interval and degree of freedom equal to 0.05 was carried out using a two-way analysis of variance (ANOVA) test. Tukey's allowable difference was calculated to find the difference between treatments. SPSS Statistics software package (version 20, IBM, Chicago, ill, USA) was used.

Results

Tables 2 and 3 show drug release against time for formulations F1 to F7 and F8 to F13, respectively. MTZ release was found to be affected by the type of polymers used in the preparation of chitosan films using 01.0% lactic acid as solvent.

Table 2: *In-vitro* release profile of metronidazole films from F1 to F7

Time (hr.)	% Metronidazole released						
	F1 80.0% Chitosan	F2 20% EC, 60.0% Chitosan	F3 60% EC, 20.0% Chitosan	F4 60% MC, 20.0% Chitosan	F5 20% MC, 60.0% Chitosan	F6 20% PVP, 60.0% Chitosan	F7 60% PVP, 20.0% Chitosan
0.0	0	0	0	0	0	0	0
0.5	7.806	16.30	18.51	5.016	1.714	5.74	9.246
1.0	27.637	53.45	89.41	37.956	11.626	14.311	30.728
1.5	40.651	72.03	100.03	43.841	18.954	35.891	53.547
2	50.261	81.67		46.216	22.567	47.662	60.878
2.5	55.528	89.93		47.662	25.462	53.651	62.53
3.0	59.04	91.30		48.591	29.386	56.129	65.215
3.5	65.441	100.6		54.683	31.145	56.232	72.276
4.0	75.154			65.525	36.304	57.161	73.37
4.5	86.823			67.59	37.021	58.24	78.53

Figures 1 and **2** depict the effect of chitosan alone and its combination with different polymers on the release of MTZ from formulations F1 to F13. The effect of the addition of each polymer is clear, and the statistical differences are shown in **Table 4**, which will be discussed in detail in the discussion part.

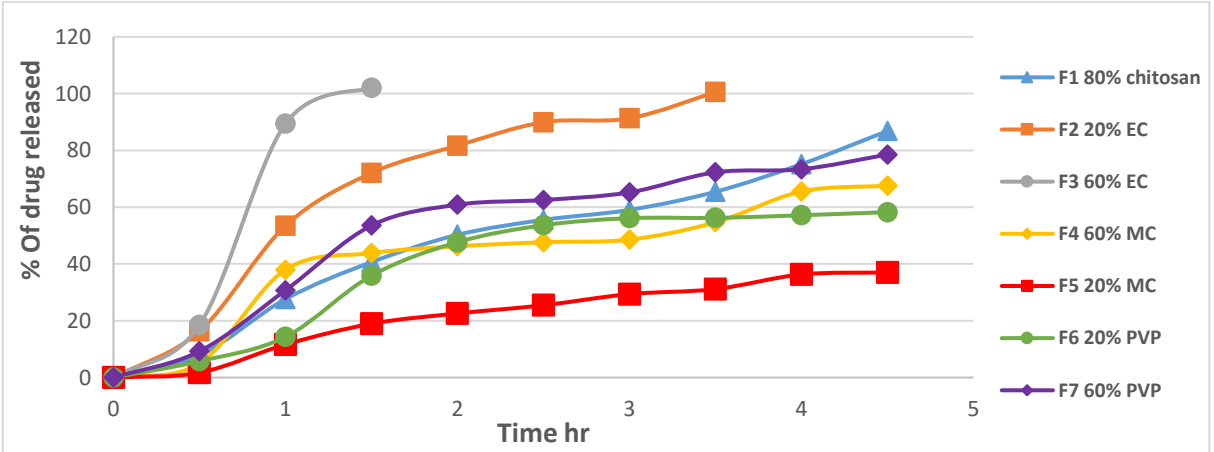

Figure1: Percentage of metronidazole released from films of formulations F1-F7

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Film surface pH study: **Table 4** shows that the pH of the surface environment of selected films is ranges from 5.01±0.11 to 6.98±0.066, indicating that the pH of formulations F1, F12, and F13 falls within the pH tolerance of the mucus membrane (pH=5.6 up 7.4).

Drug content uniformity: The drug content uniformity values were found to be between 89.35% and 96.61% of the theoretical values. The observed results of content uniformity in **Table 4** indicated that the drug was uniformly distributed throughout all selected films.

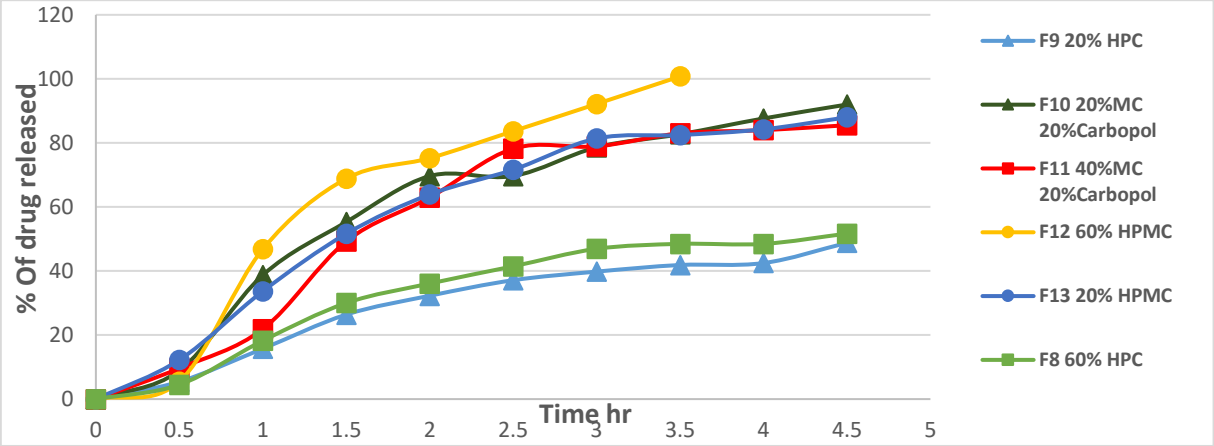

Figure 2: Percentage of metronidazole released from films of formulations F8-F13

Folding endurance: **Table 4** reveals that the tested films did not show any cracks even after folding for more than 250 times. Hence, it was taken as the endpoint.

Bio-adhesion force: For mucoadhesive strength, **Table 4** reveals that a higher force was observed in F12 and F13, which was above 45 Mn/m followed by F11>F10>F1.

Table 4: Surface pH, drug content uniformity, folding endurance and muco-adhesion of formulations

Formulation	Force of detachment Mn/m) ±S.D*	Surface PH±S.D *	Folding endurance ±S.D*	% of drug content uniformity±S. D*
F1	**32(±3.130)**	**6.7 (±0.057)**	**305(±0.200)**	**89.35(±0.150)**
F10	**33 (±2.453)**	**5.12 (±0.077)**	**312(±0.010)**	**96.61(±0.177)**
F11	**48(±2.338)**	**5.01(±0.115)**	**306(±0.029)**	**90.78(±0.098)**
F12	**49(±1.527)**	**6.86(±0.100)**	**287(±0.177)**	**93.14(±0.112)**
F13	**51(±1.290)**	**6.98(±0.066)**	**276(±0.321)**	**92.76(±0.106)**

*Average of three measurements, SD: Standard deviation

Effect of film thickness on release study: According to Higuchi's diffusion-controlled mechanism, the release rate constant (K) should be independent of film thickness. But the duration of drug release was affected by film thicknesses [23, 24]. **Table 5** shows the treatment of data after the drug release studies from formulation F13 of different thicknesses using different mechanisms of drug release.

Table 5: First-order and Higuchi treatment of data for metronidazole release from film F13 as

F13	Higuchi kinetics			First order kinetics		
Film thickness (µm)	K (mg/cm^2 min ½) Higuchi	t½ (min)	R^2	K (min−1 first order)	t½ (min)	R^2
55.75	0.0389	57.7	0.9853	0.00850	81.5	0.9814
108.35	0.0482	66.7	0.9828	0.00432	160.5	0.9814
349.8	0.265	67.4	0.9811	0.00255	271.8	0.9828

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FTIR study results: FTIR spectra of MTZ alone and its combination with polymers are shown in **Figures 3-5**. The spectra confirmed the absence of any chemical incompatibility between the drug and the polymer.

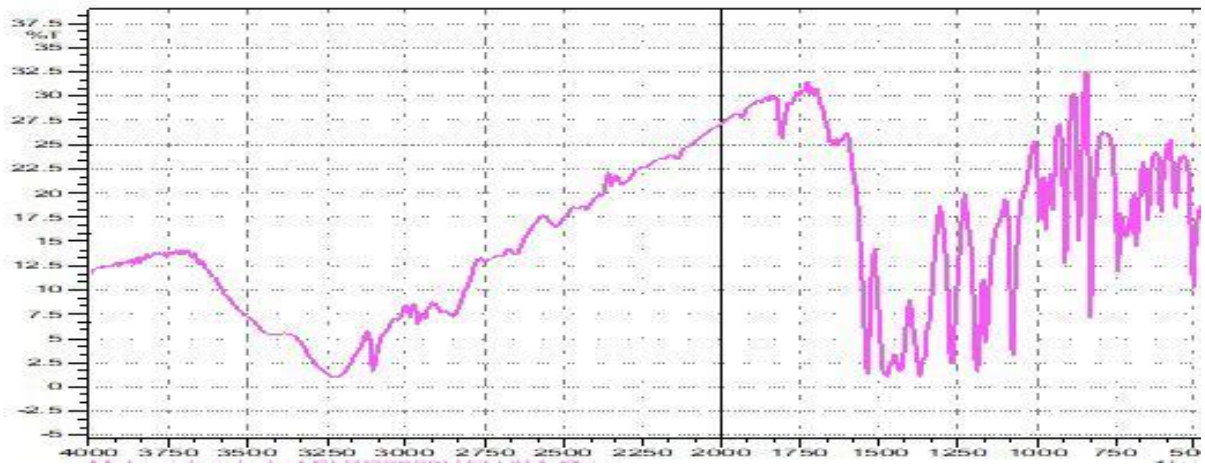

Figure 3: FTIR spectra of metronidazole standard

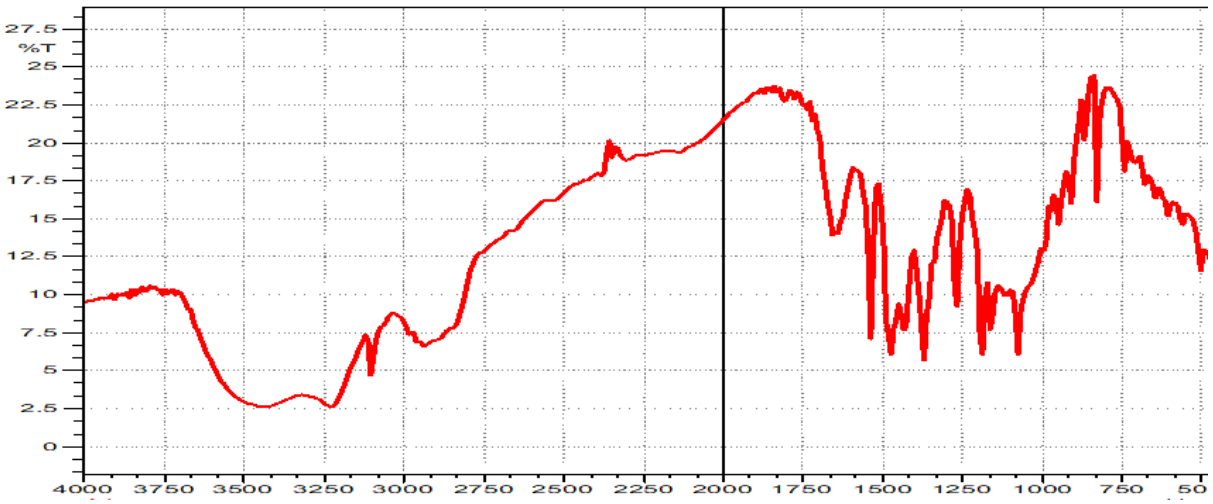

Figure 4: FTIR spectra of formulation F12 with matching score 91.0%

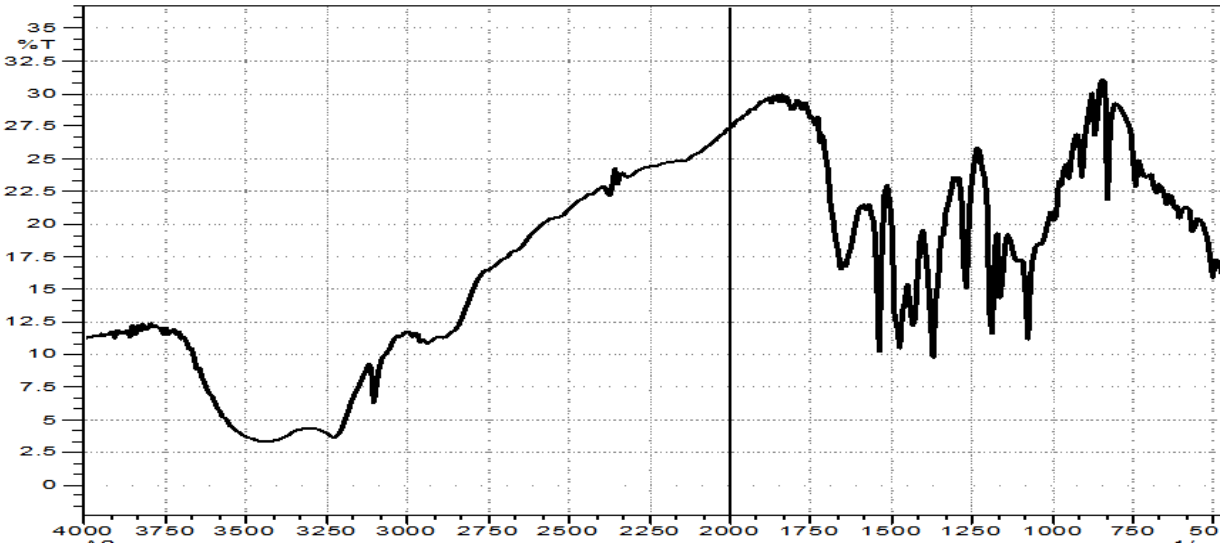

Figure 5: FTIR spectra of formulation F13 with matching score 90.5%

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Kinetic data analysis: The resulted kinetic data analysis of formulations F1-F13 are shown in **Table 6**. Below are the calculated release constants and the regression coefficient (R) for zero-order, first -order, Higuchi, and Korsmeyer-Peppas model, the best model that fitted with each film.

Table 6: Zero-order, first-order and Higuchi treatment of data for ibuprofen release from all studied films

Formulation	Zero order		First order		Higuchi model		Korsmeyer-Peppas	
	R^2	(k_0, %/hr.)	R^2	(k_1, h^{-1})	R^2	(k_h, $\frac{\%}{\sqrt{hr}}$)	R^2	k_p
F 1	0.994	20.06	0.857	0.53	0.987	44.45	0.996	K=25.35, n=0.65
F 2	0.991	28.00	0.965	0.72	0.993	50.20	0.999	K=30.10, n=0.70
F 3	0.998	68.00	0.999	1.50	0.999	80.00	0.999	K=60.00, n=0.90
F 4	0.982	16.50	0.920	0.40	0.975	30.00	0.980	K=20.00, n=0.60
F 5	0.978	8.20	0.890	0.25	0.960	15.00	0.970	K=10.00, n=0.50
F 6	0.981	12.80	0.910	0.35	0.965	23.00	0.975	K=15.00, n=0.55
F 7	0.985	18.00	0.930	0.45	0.980	32.00	0.985	K=22.00, n=0.62
F 8	0.970	13.73	0.973	0.795	0.983	24.60	0.986	K=15.97, n=1.76
F 9	0.987	9.78	0.985	0.698	0.992	18.28	0.991	K=10.64, n=1.65
F 10	0.966	20.78	0.976	0.902	0.981	36.22	0.999	K=27.30, n=1.71
F 11	0.981	19.31	0.980	0.856	0.991	33.80	0.998	K=24.50, n=1.69
F 12	0.992	32.63	0.989	1.031	0.995	50.40	0.999	K=40.10, n=1.74
F 13	0.990	19.52	0.982	0.745	0.996	34.50	0.997	K=24.80, n=1.67

Table 7 shows the statistical analysis of the data.

Table 7: Data analysis after release studies out of selected thin films

Formulations	Two- way ANOVA	Tukey's HSD test (post-hoc analysis)	
F2 & F3	Interaction effect, p=0.017 Main effect of formulation, p=0.567 Main effect of time, p=0.0015	At 0.5 hr At 1.0 hr At 1.5 hr	p=0.908 p=0.013 p=0.028
F4 & F5	Interaction effect, p<0.0001 Main effect of formulation, p<0.0001 Main effect of time, p<0.0001	Every single time measured from 0.5-4.5 hr	p<0.0001, (p< 0.05) Significant difference at every single time point measured.
F6 & F7	Interaction effect, p<0.0001 Main effect of formulation, p<0.0001 Main effect of time, p<0.0001	Every single time measured from 1-4.5 hr	p<0.0001, (p<0.05) Significant difference at every single time point measured from 1-4.5 hr
F8 & F9	Interaction effect, p=0.024 Main effect of formulation, p=0.023 Main effect of time, p<0.0001	Every single time measured from 2-4 hr	p<0.0001, (p<0.05) Significant difference at every single time point measured from 2-4 hr
F10 & F11	Interaction effect, p<0.0001 Main effect of formulation, p=0.503 Main effect of time, p<0.0001	At 1.0 hr At 1.5 hr At 2.0 hr At 2.5 hr At 3.0 hr At 4.0 hr At 4.5 hr	p=0.0001 p=0.051 p=0.023 p=0.002 p=0.987 p=0.191 p=0.032
F12 & F13	Interaction effect, p<0.0001 Main effect of formulation, p<0.0001 Main effect of time, p<0.0001	Every single time measured from 0.5-4.5 hr	p<0.0001, (p<0.05) Significant difference at every single time point measured from 0.5-4.5 hr

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Discussion

In this study, MTZ-loaded buccal films were successfully formulated using a solvent casting technique with chitosan as the primary polymer, combined with various copolymers at different ratios. FTIR spectroscopy was employed to assess potential interactions between the drug and polymeric excipients. The spectra of pure MTZ displayed characteristic peaks, which remained unaltered in the physical mixtures with chitosan and HPMC (Formulations F12 and F13). The absence of new peaks or significant shifts, coupled with a high matching score (≈90%), confirms the lack of chemical incompatibility and suggests that the drug and polymers are suitable for film formulation. The surface pH of the films is a critical parameter, as deviations from neutrality can cause mucosal irritation and affect polymer hydration. The measured surface pH for films F1, F12, and F13 ranged between 6.0 and 7.0, which is acceptably close to the pH of gingival crevicular fluid (≈6.6). This indicates a low potential for mucosal irritation, a finding consistent with established literature on buccal dosage forms [7, 26].

All selected formulations exhibited excellent mechanical properties, with folding endurance values exceeding 250 folds, indicating the formation of flexible and robust films suitable for buccal application [7]. Furthermore, drug content uniformity analysis revealed values between 89.35% and 96.61%, demonstrating a homogeneous distribution of MTZ within the polymeric matrices. The bio-adhesive strength of the films was found to be highly dependent on the nature and concentration of the polymers. Films F12 and F13 composed of chitosan and HPMC, required the maximum force for detachment (49 and 51 mN/m, respectively), with no significant difference between them. This superior mucoadhesion can be attributed to chitosan's amine and hydroxyl groups, which strongly interact with the negative charges of mucin at neutral pH, reinforcing the adhesive interface. This result aligns with findings from Mahapatra et al. [27] and Gaber et al. [28]. Formulations containing only chitosan or blends with MC and carbopol exhibited statistically lower adhesive forces. The impact of film thickness on drug release was investigated using formulation F13. The results demonstrated an inverse relationship; as thickness increased from 55.75 µm to 349.8 µm, the release rate constant (K) decreased, and the half-life ($t_{½}$) increased significantly. This finding could be explained by the fact that thinner films facilitate faster drug release due to shorter diffusion pathways, while thicker films provide a more sustained release profile, a phenomenon well-documented in drug delivery literature [29, 30]. The high correlation coefficients (R^2=0.98) for Higuchi and first-order models indicate the applicability of these kinetics, with the Higuchi model providing a slightly better fit, suggesting a diffusion-controlled release mechanism. This supports the work of Elkomy et al. [31] on MTZ floating tablets. The *in vitro* drug release profiles from the thirteen formulations (F1-F13) were profoundly influenced by the type and ratio of polymers used: Chitosan alone (F1) formed a flexible, elastic film but provided a sustained release (87.0% in 4.5 hr), attributable to its gel-forming ability and viscous matrix, which slows diffusion [32]. EC blends (F2, F3), particularly F3 with a high EC ratio, showed rapid release (complete by 1.5-2 hr), due to EC's poor swelling and limited mucoadhesion, reducing the matrix barrier effect [33]. MC blends (F4, F5) exhibited intermediate release rates. F5, with a high MC content, showed a more controlled release than EC systems, suggesting MC contributes to swelling and gel formation [30]. PVP blends (F6, F7): The significant difference in drug release between F6 and F7 is attributed to the polymer ratio. Excess PVP (F6) created a highly soluble matrix leading to erosion and slower release, whereas a balanced ratio with chitosan (F7) optimized solubility with muco-adhesion [34-37]. HPC blends (F8, F9) displayed the most sustained profiles. F9 released only 48.8% in 4.5 hours. The combination of HPC's viscous gel-forming nature and chitosan's properties created a dense hydrogel barrier that significantly retarded drug diffusion [38]. HPMC blends (F12, F13): Formulation F12 (60.0% HPMC) demonstrated the fastest and most complete release (100% in 3.5 hr). Despite being a gel-forming polymer, HPMC's specific properties at high concentration promoted rapid hydration and erosion rather than a sustained barrier. This highlights that release is dependent not only on polymer type but also on

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its molecular weight and concentration [39]. Carbopol blends (F10, F11) showed an interesting intermediate profile. Carbopol's excellent muco-adhesion and high swelling capacity created a structured gel. F11 exhibited a more sustained release than F10, indicating that a balanced ternary system of swelling polymers (MC, Carbopol) with a mucoadhesive agent (chitosan) is optimal for extended release [34].

Based on the kinetic analysis of the 13 MTZ buccal film formulations, the predominant mechanism of drug release is best described by the Korsmeyer-Peppas model in which formulations F1 to F7 follow a mixed mechanism of diffusion and polymer relaxation (anomalous transport or non-Fickian diffusion) and formulations F8 to F13 in which (n>1) indicative of super case-II transport, a mechanism dominated by polymer relaxation, swelling and eventual erosion of the polymeric matrix. The Higuchi model also showed an excellent fit (R^2 from 0.931 to 0.996), suggesting that diffusion through a swollen matrix plays a significant role in the release process for most films. This understanding is crucial to conclude that by modifying polymeric composition the release profile can be tailored to achieve the desired therapeutic outcome, whether it is designed to be immediate or sustained release for buccal delivery of MTZ.

Conclusion: Metronidazole dental films were prepared by the solvent casting technique using chitosan and various copolymers. FTIR and pH analysis confirmed the chemical and mucosal compatibility. All tested films showed good flexibility and uniform drug distribution. The *in vitro* release kinetics of metronidazole can be precisely engineered thought strategic polymer selection and ratio optimization, enabling tailored release profiles for either immediate or prolonged therapeutic action. The drug release mechanism followed the Korsmeyer-Peppas model.

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